CCA-431

547.495.1.07

*Note*

# The Synthesis of Some Disubstituted Derivatives of *p,p'*-bis- (Pyrimidyl-2-sulphamyl)-carbanilide. II*

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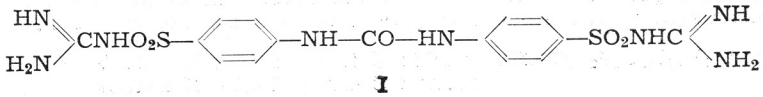
Received April 15, 1966

In an earlier paper[1] we described the preparation of some disubstituted derivatives of *p,p'*-bis-(sulphamyl)-carbanilide by the condensation of carbanilide-*p,p'*-disulphonic acid dichloride with various heterocyclic amines, and their hydrolysis to the corresponding sulphonamides. This paper reports our work concerned with the synthesis of *p,p'*-bis-(pyrimidyl-2-sulphamyl)-carbanilides by condensation of *p,p'*-bis-(*N*-guanylsulphamyl)-carbanilide with various appropriate substituted aliphatic carbonyl compounds. The preparation was performed according to the standard procedures for the synthesis of substituted sulphapyrimidines[2-4] and pyrimidines[5].

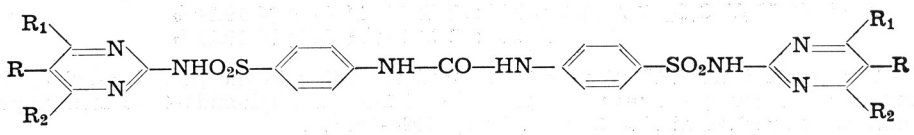


I

The starting material was *p,p'*-bis-(*N*-guanylsulphamyl)-carbanilide (I) which has not been previously described. It was prepared by the condensation of carbanilide-*p,p'*-disulphonic acid dichloride and guanidine nitrate in the presence of sodium hydroxide by the somewhat modified procedure given by Richmond[6] for the preparation of sulphaguanidine. All carbonyl compounds used in our experiments have been prepared earlier, except α-methoxy-β--dimethylaminoacrolein which has not been isolated and characterized until now. We prepared it under the conditions of the Vilsmeier-Haack[7] reaction modified by Arnold and Šorm[4,8].

TABLE I

*Prepared Substituted* p,p'*-bis-Pyrimidyl-2-sulphamyl)-carbanilides*



| | R | $R_1$ | $R_2$ | | R | $R_1$ | $R_2$ |
|---|---|---|---|---|---|---|---|
| II | H | $CH_3$ | H | **V | $OCH_3$ | OH | H |
| III | H | $CH_3$ | $CH_3$ | VI | $OCH_3$ | Cl | H |
| IV | $OCH_3$ | H | H | | | | |

* Yug. pat. appl. P-911/65.

** Compound V was converted into the corresponding 4-chloro derivate (VI) by treatment with phosphorus oxychloride.

Compounds II—IV gave the corresponding sulphonamides by alkaline hydrolysis[1].

## EXPERIMENTAL

All melting points are uncorrected.

### p,p'-*Bis-(N-guanylsulphamyl)-carbanilide* (I)

A solution of carbanilide-*p,p'*-disulphonic acid dichloride[1] [prepared from 144 g. (0.68 mole) of carbanilide and 450 ml. (6.8 moles) of chlorosulphonic acid] in 1300 ml. of methyl-ethyl ketone was gradually added, with vigorous stirring, over a period of 3 hrs. at 0—5° to a mixture prepared from 129 g. (1.05 moles) of guanidine nitrate, 201.5 g. (8.8 moles) of sodium hydroxyde, 474 ml. of water and 450 ml. of methyl-ethyl ketone. The reaction mixture was stirred for an additional hr. at the same temperature, the solid filtered off by suction and washed with water. The yield was 200 g. (64.6%) of crude product; colourless crystals (several times from diluted ethanol), m.p. 278°.

*Anal.* $C_{15}H_{18}N_8O_5S_2$ (454.479) calc'd.: C 39.65; H 3.97; N 24.67%
found : C 39.83; H 4.19; N 24.75%

### p,p'-*Bis-(4-methylpyrimidyl-2-sulphamyl)—carbanilide* (II)

A mixture prepared from 6.64 g. (0.123 mole) of sodium methylate, 1000 ml. of methanol, 13.6 g. (0.03 mole) of crude *p,p'*-bis-(*N*-guanylsulphamyl)-carbanilide and 8.4 g. (0.0636 mole) of 3-ketobutyraldehyde dimethylacetale as heated under reflux for 4.5 hrs. After evaporation of the solvent the residue was dissolved in 150 ml. water, and the solution acidified with acetic acid to *p*H 5—6. The yield was 15 g. (91.5%) of crude product which was dissolved several times in dimethylformamide and reprecipitated with methanol to give a colourless solid, m.p. 270°.

*Anal.* $C_{23}H_{22}N_8O_5S_2$ (554.590) calc'd.: C 49.80; H 4.00; N 20.22%
found : C 49.80; H 4.18; N 20.03%

The crude product II (6.1 g.) was hydrolysed as described earlier[1] to yield 5.6 g. (96.3%) of crude 2-sulphanilylamido-4-methyl pyrimidine which melted at 220—225°. After purification[1], the melting point rose to 233—236° (lit.[9] m.p. 232°).

### p,p'-*Bis-(4,6-dimethylpyrimidyl-2-sulphamyl)-carbanilide* (III)

A mixture of 54.4 g. (0.12 mole) of *p,p'*-bis-(*N*-guanylsulphamyl)-carbanilide, 48 g. (0.48 mole) of acetylacetone and 3.2 ml. of glacial acetic acid was heated for 20 hr. at 115—120°. After cooling, the reaction mixture was dissolved in 400 ml. of 5% sodium hydroxide solution, filtered (charcoal), and acidified with acetic acid to *p*H 6. The product was purified by repeating the above precipitation procedure. The yield was 54 g. (77.5%) of crude product which was dissolved several times in a mixture of methoxyethanol-ethylacetate-methanol (1:1:1), and reprecipitated with water to give a colourless solid, m.p. 265—267°.

*Anal.* $C_{25}H_{26}N_8O_5S_2$ (582.642) calc'd.: C 51.53; H 4.49; N 19.24%
found : C 51.30; H 4.22; N 19.11%

The product III (17.5 g.) was hydrolysed according to the procedure given for compound II[1]. The yield was 15.1 g. (90%) of 2-sulphanilylamido-4,6-dimethylpyrimidine which melted at 198—200° (lit.[10] m.p. 199—200°).

### α-*Methoxy*-β-*dimethylaminoacrolein*

The preparation was carried out by a slight modification of the method given in the patent of Priewe and Gutsche[4]. Phosphorus pentachloride 21 g. (0.1 mole) was gradually added with stirring at 20—30° to 12 g. (0.1 mole) of 1,1,2-trimethoxyethane, and the reaction mixture heated for 75 minutes at 60°. After cooling and the addition of 225 ml. (0.29 mole) of dimethylformamide at 0—10°, the stirring was continued for 40 hrs. at room temperature, and then 100 ml. (2.47 moles) of methanol were added

at 0—10°. The darkly red coloured reaction mixture was added dropwise with stirring at 15—20°C to a solution of 40 g. (0.74 mole) of sodium methylate in 275 ml. of methanol. After boiling for 4 hr. the solvent, and the dimethylamine formed during the reaction were evaporated, the residue dissolved in 70 ml. of methanol, and saturated with dry gaseous hydrochloric acid. The precipitate was removed by suction, the mother liquor evaporated, and the residue distilled *in vacuo* to give 6 g. (46.5%) of a thick oil, b. p. 95—105°/0.4 mm. This oil was dissolved in ether, the ethereal solution cooled to —70°, the formed crystals separated by decantation from the mother liquors, and after several repetitions of this procedure the separated product was finally distilled as a light yellow oil at 100—102°/0.35 mm.

*Anal.* $C_6H_{11}NO_2$ (129.156) calc'd.: C 55.79; H 8.58; N 10.85%
found : C 55.64; H 8.40; N 10.97%

Picric acid 2.29 g. (0.01 mole) in 15 ml. of dioxane was added to a solution of 1.2 g. (0.01 mole) of crude α-methoxy-β-dimethylaminoacrolein in 5 ml. of dioxane, and kept in an ice box for 12 hrs. The yield was 0.8 g. (22.3%) of crude picrate; lemon yellow crystals (from ethylacetate), m.p. 103—104°.

*Anal.* $C_{12}H_{14}N_4O_9$ (358.26) calc'd.: C 40.23; H 3.94; N 15.64%
found : C 40.00; H 4.05; N 15.82%

### p,p'-*Bis-(5-methoxypyrimidyl-2-sulphamyl)-carbanilide (IV)*

A solution of 1.2 g. (0.022 mole) of sodium methylate, 30 ml. of methanol, 4.5 g. (0.01 mole) of *p,p'*-bis-(*N*-guanylsulphamyl)-carbanilide and 2.58 g. (0.02 mole) of the crude oily α-methoxy-β-dimethylaminoacrolein obtained as described above was boiled for 4 hrs. and evaporated to dryness. The residue was dissolved in 30 ml. of water, the solution filtered (charcoal) and acidified with acetic acid to pH 6. The yield was 5 g. (86.2%) of crude product which was dissolved several times, in a mixture of methoxyethanol-ethylacetate (1 : 1) and reprecipitated with water to give the analytical sample, m.p. 272—275°.

*Anal:* $C_{23}H_{22}N_8O_7S_2$ (586.602) calc'd.: C 47.09; H 3.78; N 19.10%
found : C 46.85; H 3.52; N 19.04%

The crude product IV (5 g.) was hydrolized according to the procedure given for compound II[1]. The yield was 3.53 g. (73.2%) of 2-sulphanilylamido-5-methoxypyrimidine, m.p. 212—213° (lit.[11] m.p. 212—214°).

### p,p'-*Bis-(4-hydroxy-5-methoxypyrimidyl-2-sulphamyl)-carbanilide (V)*

A mixture of 91 g. 0.2 mole) of *p,p'*-bis-(*N*-guanylsulphamyl)-carbanilide, 23 g. (0.426 mole) of sodium methylate and 3000 ml. of methanol was added to the crude dry methyl sodium-β-hydroxy-α-methoxy acrylate[5] prepared from 9.8 g. (0.426 atome) of sodium, 44.2 g. (0.424 mole) of methyl methoxyacetate and 31.4 g. (0.424 mole) of ethyl formiate in 200 ml. of toluene. The reaction mixture was refluxed for 6 hr., evaporated to dryness, and the residue dissolved in 650 ml. of water. After cooling at 15° the unreacted *p,p'*-bis-(*N*-guanylsulphamyl)-carbanilide (12 g.) was removed by filtration, and the filtrate acidified with acetic acid to pH 6. The yield was 91 g. (84.5%) of crude product which was dissolved several times in dimethylformamide and reprecipitated with water to give a colourless solid, m.p. 288—290°.

*Anal.* $C_{23}H_{22}N_8O_9S_2$ (618.59) calc'd.: C 44.68; H 3.56; N 18.10%
found : C 44.91; H 3.40; N 18.25%

### p,p'-*Bis-(4-chloro-5-methoxypyrimidyl-2-sulphamyl)-carbanilide (VI)*

The preparation was carried out according to the procedure described by Nováček *et al.*[11] from 19.8 g. (0.032 mole) of crude V with 20 ml. of phosphorus oxychloride and 5 ml. of pyridine. The yield was 21 g. (100%) of crude product, m.p. 270—275°. Colourless crystals (from dilute dimethylformamide), m.p. 283—285°.

*Anal:* $C_{23}H_{20}Cl_2N_8O_7S_2$ (655.488) calc'd.: C 42.15; H 3.07; N 17.08%
found : C 42.11; H 3.30; N 17.23%

*Acknowledgment.* The authors are grateful to Mr. E. Guštak for his continous interest in this work, and for helpful discussions.

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## IZVOD

**Sinteza nekih disupstituiranih derivata p,p'-bis-(pirimidil-2-sulfamil)-karbanilida. II.**

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Kondenzacijom diklorida karbanilid-*p,p'*-disulfonske kiseline i gvanidina pripravljen je *p,p'*-bis-(*N*-guanilsulfamil)-karbanilid (I) iz kojeg su kondenzacijom s odgovarajućim supstituiranim karbonilnim spojevima dobiveni *p,p'*-bis-(4-metil--pirimidil-2-sulfamil)-karbanilid (II), *p,p'*-bis-(4,6-dimetilpirimidil-2-sulfamil)-karbanilid (III), *p,p'*-bis-(5-metoksipirimidil-2-sulfamil)-karbanilid (IV) odnosno *p,p'*-bis--(4-hidroksi-5-metoksipirimidil-2-sulfamil)-karbanilid (V). Ovaj posljednji je obradom s fosforoksikloridom preveden u odgovarajući 4-klor derivat (VI). Izoliran je čisti α-metoksi-β-dimetilaminoakrolein i karakteriziran kao pikrat. Spojevi II—IV su alkalnom hidrolizom prevedeni u odgovarajuće dobro poznate sulfonamide.

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ZAGREB

Primljeno 15. travnja, 1966.